Amendment of the claims:

Claims 45-47 and 54-60 are amended by removing the limitation that the claimed composition is a pharmaceutical composition. The amended claims are simply directed to compositions comprising the recited anti-CD23 antibody. Such compositions comprising the claimed antibodies are described in the specification; for example, on page 69, which describes their use in an in vitro assay for inhibition of IgE induction. The specification also demonstrates using a composition comprising anti-CD23 antibodies that have been shown to bind to a particular CD23 epitope in an in vitro competition assay to identify a CD23 epitope that is bound by an anti-CD23 antibody of undetermined epitope specificity (paragraph bridging pp 36-37). Persons skilled in the art would recognize that the claimed compositions can be used in like fashion. New claims 61-70 are dependent on claims 45-47 and 54-60, respectively, and recite that the claimed composition is a pharmaceutical composition. New claims 61-70 are directed to the same subject matter and have the same scope as claims 45-47 and 54-60 submitted in the amendment filed February 25, 2002. Claim 49 is amended to correct a misspelling. No new matter is added by the amendment.

Rejection under 35 U.S.C §112, 1st paragraph:

Claims 42-60 were rejection under 35 U.S.C §112, 1st paragraph, on the grounds that the specification is enabling for (a) the claimed anti-human CD23 antibodies wherein the variable domains "consist of" the recited polypeptides encoded by disclosed DNA sequences; but not for the claimed anti-CD23 antibodies "comprising" said polypeptides, and (b) a composition comprising the disclosed antibodies and a phamaceutical carrier; but it does not describe or enable the claimed anti-CD23 antibodies "comprising" said polypeptides, or a pharmaceutical composition comprising the disclosed antibodies. As support for the rejection of the claims that recite anti-CD23 antibodies with variable regions "comprising" the disclosed polypeptides, the office action notes that the term "comprising" is open-ended, and that the claims encompass anti-CD23 antibodies with variable regions that contain the disclosed polypeptides plus one or more additional amino acids at either or both ends. It notes that the present application discloses 5 murine and 6 primate anti-CD23 antibodies. The office action refers to an article by Abaza et al. that shows that mutation of an antibody at sites outside of the variable region can abolish specific binding, and to an article by Skolnick

et al. that discusses the unpredictability of protein folding; and concludes the claimed anti-CD23 antibodies with variable regions "comprising" the disclosed polypeptides are not described, and that undue experimentation would be required to make and use the claimed anti-CD23 antibodies.

The Applicants traverse these grounds of rejection, and respectfully submit that the claimed invention is described by the specification so that persons skilled in the art are able to follow the disclosure and make and use the claimed anti-CD23 antibodies and pharmaceutical compositions without undue experimentation.

With regard to the use of "comprising":

All of the claims recite an "anti-CD23 antibody;" i.e., the claims are inherently directed to antibodies that bind specifically to CD23. The application provides an example showing how to introduce a mutation (substitution) into the amino acid sequence of one of the diclosed antibody polypeptides (e.g., the gamma-4 constant region), and describes assays for determining the affinity with which the resultant modifed antibody binds to CD23. The Abaza et al. reference also describes methods for changing the amino acid sequence of an antibody and for screening to determine whether the change affects the affinity of the antibody for its target. At the time the present application was filed, persons skilled in the art would have been able to follow the disclosed teachings and make the claimed anti-CD23 antibodies with variable regions comprising the disclosed polypeptides with one or more additional residues at either end, and then screen them to identify antibodies having suitable affinity for CD23. Persons skilled in the art know that it is often difficult to predict whether a given change will disrupt the 3-dimensional structure of the antigen binding site. However, the present application shows that heavy chain variable regions of both primate antibodies 5E8 and 6G5 bind effectively to CD23, whether they are attached to either monkey or human gamma-1 or gamma-4 constant chains (e.g., see Example 1, pp. 68-69 and Figs. 3-5; and Example 3, p. 73 and Figs.8-10). One skilled in the art would recognize that the attachment of the variant monkey and human gamma-1 and gamma-4 chains to the ends of the disclosed CD23-specific variable sequence polypeptides as shown in the disclosed Examples is predictive of the effect of adding one or more different residues to ends of the variable sequences. Persons skilled in the art would therefore consider the data in the application as good evidence that CD23-specific antibodies encompassed by the present claims can be

obtained using the disclosed methods without undue experimentation. The Abaza et al. article cited in the rejection must be considered in its proper scientific context. At the time Abaza et al. was published (1992), it was known from studies carried out in the '70s and '80s that amino acid substitutions could be made in an antibody outside of the critical portions of the variable regions without significantly altering the binding affinity, and amino acid mutations that reduced binding affinity were assumed to be physically located in the antigen-binding portion of the antibody (see pp. 437-8). This is noted and discussed briefly in the specification with regard to mutations in the constant regions (pp. 61-62). The significance of the Abaza et al. reference lies in its demonstration that mutations outside of the variable region can cause a large reduction in binding affinity. However, this finding does not negate the previously established recognition of those skilled in the art that residues outside of the critical portions of the variable regions can be altered without significantly altering the antibody's affinity for CD23. The view that persons skilled in the art would be able to make and use antibodies such as those that are claimed without having to perform undue experimentation also appears to be one that the U.S. Patent and Trademark Office has held with respect to antibodies of similar structure that are described by disclosures similar to the present application. For example, the Examiner's attention is directed to co-owned U.S. Patent No. 6,136,310 issued October 24, 2000, in which claim 1 recites:

> " 1. A chimeric antibody specific to human CD4 which comprises the variable light chain sequence set forth in SEQ. ID. NO. 5 and a heavy chain sequence selected from the group consisting of the gamma-4 heavy chain sequence set forth in SEQ. ID. NO. 7, the gamma-4 heavy chain sequence set forth in SEQ. ID. NO. 9, and the gamma-4 heavy chain sequence set forth in SEQ. ID. NO. 11."

Similarly, claim 1 of co-owned U.S. Patent No. 6,001,358 issued December 19, 1999, recites:

> " 1. A humanized antibody or antigen-binding fragment thereof that specifically binds the CD40 ligand wherein said humanized antibody or fragment thereof contains a variable light sequence which comprises the amino acid sequence encoded by the nucleic acid sequence having SEQ ID No. 24 or SEQ ID No. 25 and the said humanized antibody or fragment thereof contains a variable heavy sequence which comprises the amino acid sequence encoded by the nucleic acid sequence having SEQ ID No. 26."

While every application must be examined on its merits, the recent allowance by the U.S. Patent and Trademark Office of claims to antibodies using "comprising" language as shown in the above two examples, can be regarded as additional evidence that antibodies encompassed by such claims can be made and used by those skilled in the art without undue experimentation. Accordingly, the Applicants respectfully request that the rejections of the claims under 35 U.S.C §112, 1st paragraph, on the grounds that they recite antibodies using "comprising" language be withdrawn.

With regard to claims to a pharmaceutical composition:

As support for the rejection of the claims that recite a pharmaceutical composition comprising the disclosed antibodies, the office action cites Van Noort et al. for the teaching that autoimmune diseases are species and model-dependent; it asserts that there many different types of autoimmune diseases, and that it is unpredictable which "undisclosed" antibodies would be useful for treating any autoimmune disease; it observes that chimeric anti-CD23 antibodies are not listed in the Merck Manual; and it states that the data in Figures 9 and 10 suggests that the disclosed anti-CD23 antibodies are no more active than control antibodies, so that undue experimentation would have been required to make or use the claimed invention.

The Applicants respectfully traverse the rejection under 35 U.S.C §112, 1st paragraph, for non-enablement of the claimed pharmaceutical composition. In the first place, the office action misrepresents the data in Figures 9 and 10. As discussed in Example 3 (see p. 73, lines 12-15), Figure 10 compares the IgE-inhibiting activity in the hu-SCID mouse model of the primate 6G5 and the primatized p6G5G1 antibody recited in claims 42, 43, 45 and 46. Figure 10 clearly shows that the p6G5G1antibody efficiently inhibits IgE production in hu-SCID mice. The absence of a reference to anti-CD23 antibodies in the Merck Manual is immaterial here, since the criteria for satisfaction of 35 U.S.C §112, 1st paragraph, are different from those used to obtain listing in the Merck Manual. With respect to enablement of pharmaceutical use, the disclosed experimental data demonstrates that the claimed composition acts as a drug to inhibit IgE production in experimental hu-SCID mice that have human immune systems. Persons skilled in the art would regard the disclosed experimental data as providing a reasonable expectation that administration of the claimed pharmaceutical

composition comprising the disclosed primatized anti-CD23 antibodies would similarly inhibit IgE production in a human. As taught in the specification, it is well known that many pathological conditions (e.g., asthma, allergic rhinitis, atopy) are mediated by IgE (see pages 75-78), and suppression of IgE synthesis in a patient with such a condition is generally regarded as a therapeutic strategy for treating the condition. Accordingly, persons skilled in the art would reasonably expect that administration of the claimed pharmaceutical composition comprising the disclosed primatized anti-CD23 antibodies to a person suffering from an IgE-mediated pathological condition such as those any of described in the specifiction would provide therapeutic benefit to the treated individual. The official action fails to provide scientific evidence that would cause one skilled in the art to doubt the therapeutic efficacy of the claimed pharmaceutical composition. The Applicants submit that the requirements of 35 U.S.C §112, 1st paragraph, are met by the present application and claims drawn to a pharmaceutical composition; and therefore respectfully request withdrawal of the rejections of the claims reciting under 35 U.S.C §112, 1st paragraph.

Rejection under 35 U.S.C §112, 2nd paragraph:

Claims 49 and 53 were rejected under 35 U.S.C §112, 2nd paragraph, as being indefinite because the word "codon" in claim 49 was misspelled, and no antecedent basis was found in claim 49 for the reference in claim 53 to a human constant gamma-3 region.

The Applicants appreciate identification of the misspelled word in claim 49, which is corrected by the amendment above. The rejection of claim 53 as being indefinite is respectfully traversed. Claim 49 is drawn to an anti-human CD23 antibody with light and heavy variable regions comprising specific polypeptides. Claim 53 depends on claim 49, and further recites that the anti-human CD23 antibody of claim 49 comprises a human gamma-3 constant region. The recitation of a gamma-3 constant region in claim 53 is not of a form that requires antecedent basis in claim 49. The precise metes and bounds of claim 53 are clear to persons skilled in the art. Accordingly, withdrawal of the rejections under 35 U.S.C §112, 2nd paragraph, is respectfully requested.

The Applicants appreciate the indication by the office action that the claims are free of the prior art.

The above amendment and remarks are fully responsive to the Office Action. If there are any issues remaining that need to be resolved, the Examiner is respectfully requested to contact the undersigned so that allowance of this application can be expedited.

Respectfully submitted,

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APPENDIX

IN THE SPECIFICATION:

The first paragraph on page 1 is amended as follows:

This application is a continuation-in-part of U.S. Application [Serial] No. 08/803,085, filed February 20, 1997, now U.S. Patent No. 6,011,138, issued January 4, 2000.

IN THE CLAIMS:

Claims 45-47, 49 and 55-60 are amended as follows:

45. (Amended) A [pharmaceutical] composition containing an anti-human CD23 antibody according to claim 42 and a pharmaceutically acceptable carrier.

46. (Amended) A [pharmaceutical] composition containing an anti-human CD23 antibody according to claim 43 and a pharmaceutically acceptable carrier.

47. (Amended) A [pharmaceutical] composition containing an anti-human CD23 antibody according to claim 44 and a pharmaceutically acceptable carrier.

49. (Amended) A chimeric anti-human CD23 antibody wherein the variable light domain comprises the polypeptide encoded by SEQ ID NO: 3 and the variable heavy domain comprises the polypeptide encoded by SEQ ID NO: 4 with the exception that the asparagine [colon] codon at position 75 is replaced with a lysine.

54. (Amended) A [pharmaceutical] composition comprising an anti-human CD23 antibody according to claim 48 and a pharmaceutically acceptable carrier.

55. (Amended) A [pharmaceutical] composition comprising an anti-human CD23 antibody according to claim 49 and a pharmaceutically acceptable carrier.

56. (Amended) A [pharmaceutical] composition comprising an anti-human CD23 antibody according to claim 50 and a pharmaceutically acceptable carrier.

57. (Amended) A [pharmaceutical] composition comprising an anti-human CD23 antibody according to claim 51 and a pharmaceutically acceptable carrier.

58. (Amended) A [pharmaceutical] composition comprising an anti-human CD23 antibody according to claim 52 and a pharmaceutically acceptable carrier.

59. (Amended) A [pharmaceutical] composition comprising an anti-human CD23 antibody according to claim 53 and a pharmaceutically acceptable carrier.

60. (Amended) A [pharmaceutical] composition comprising an anti-human CD23 antibody according to claim 54 and a pharmaceutically acceptable carrier.